MICRONIZED GRISEOFULVIN*

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The value of orally administered griseofulvin as an effective antifungal agent has been adequately documented (1, 2, 3). In the initial studies with commercially available griseofulvin, it was observed that, regardless of the amount of drug administered, the blood levels were very low and the amount excreted in the urine was quite small (3). This phenomenon is probably due to the fact that the drug is relatively insoluble in aqueous fluids and that there is probably little absorption from the gastrointestinal tract.

By an improved process of micronization, the particle size of griseofulvin was decreased to approximately one-third its original size. Serum levels on patients treated with micronized griseofulvin were approximately equivalent to concentration obtained with twice the dose of ordinary griseofulvin.

This study was initiated to determine whether or not micronized griseofulvin is more effective in clinical application than ordinary griseofulvin.

THE STUDY

The drug. Micronized griseofulvin ($C_{17}H_{17}O_6Cl$) is an odorless white thermostable powder. It has a total surface area value at least three or more times that of the common pharmaceutical grade. It is prepared by a special dry milling procedure, and is relatively insoluble in water and olive oil but it is soluble in ethyl alcohol, carbowax 300, chloroform, acetone, and butyl acetate. For patient administration, it was dispensed in gelatin capsules, each containing 125 mg. of micronized griseofulvin.

Patient selection. The clinical studies were performed on ambulatory patients in the author's private practice and the out-patient clinic at the University Hospital.

Dosage schedule. Each adult patient, regardless of age or weight, was given a total daily dose of 0.5 grams of micronized griseofulvin in four equally divided doses. Initially, children were given 0.375 grams of micronized griseofulvin as a total daily dose.

RESULTS

Tinea capitis. Thirty one patients with tinea capitis were treated with micronized griseofulvin. Two of these had infections due to *Microsporum canis* and 29 to *Microsporum audouini*. Diminution of fluorescence and new hair growth were observed in all instances in the third week of continuous treatment, and in 5 weeks the infection was clear. No adverse reactions were encountered in this group.

Onychomycosis. Four patients with onychomycosis were treated with orally administered micronized griseofulvin. In all instances the infection was due to *Trichophyton rubrum.* Each patient received 0.5 grams of the drug in four divided doses each day until treatment was completed. In all patients the fingernails began to show improvement 3 to 4 weeks after initiation of treatment and new fingernail growth was complete within 5 to 6 months. The toenails showed slight improvement at the end of 6 months of continuous treatment but the results were not striking.

Tinea cruris. Micronized griseofulvin, 0.5 grams per day in divided doses, was administered to 5 patients who had tinea cruris due to *Trichophyton rubrum.* Where itching was a major factor, the symptom was relieved within 48 to 72 hours after initiation of treatment. Clinical improvement became apparent in one week and in all cases involution of lesions was complete in 4 to 6 weeks.

Tinea corporis. Nine patients who had tinea corporis due to *Trichophyton rubrum* were treated with micronized griseofulvin, 0.5 grams per day in divided doses. The infection in these patients had been present for periods ranging from 6 months to 20 years. Following administration of medication, the itching subsided in 24 to 48 hours. Clinical improvement was noted during the first week of treatment and involution of lesions was complete in 5 to 8 weeks. It became necessary to discontinue administration of micronized griseofulvin to one patient because of severe frontal headaches. When the available commercial griseofulvin was administered, the headache disappeared and when the micronized griseofulvin was readministered the headache recurred.

Toxicity. One patient complained of mild diarrhea while receiving micronized griseofulvin but it was not severe enough to necessitate cessation of the treatment. One patient had severe frontal headaches whenever she took micronized griseofulvin but did not have this reaction when she received the commercial variety.

REMARKS

In the clinical studies performed with standard griseofulvin (3, 4, 5), the results indicated that a dose of less than 1 gram per day for adults was inadequate and for children it was necessary to use from 750 mg. to 1 gm. to achieve satisfactory results (3, 4, 5). In the present study using micronized griseofulvin, it is obvious that a satisfactory clinical result can be obtained with a total daily dose of 0.5 gms. of the drug, indicating that mg. for mg. micronized griseofulvin has apparently twice the efficacy of standard griseofulvin.

In the original study with griseofulvin, it was

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observed that oral administration of the drug did not result in impressive levels in blood or urine when considered in relation to the quantity given. It was theorized that this might be due to the low solubility of the agent in aqueous fluids and limited absorption from the gastrointestinal tract. A daily dose of 1 gm. of griseofulvin produced a concentration of 0.5 micrograms per ml. of plasma. These studies were made with the Beckman Model DU spectrophotometer (3). The concentrations obtained in this study varied slightly but in no instance reached the level of one microgram per ml. The studies performed with micronized griseofulvin by Kraml and Dubuc indicated that a dose of 0.5 gms would produce serum levels "indistinguishable from those obtained with 1 gm. of common pharmaceutical grade griseofulvin." They also observed that 1.0 gm. of micronized griseofulvin administered orally produced serum levels 1.7 times higher than an equal dose of common grade griseofulvin (6).

Kraml and Dubuc reported (6) that their results conclusively demonstrated that common pharmaceutical grade griseofulvin when given orally is only partly absorbed. In view of the fact that micronized griseofulvin differs only from the common grade by its particle size, they both follow the same pathways of tissue deposition, metabolism and urinary excretion. In order to rationalize the two-fold increment of serum level, they postulated it was due to increased absorption from the gastrointestinal tract.

SUMMARY AND CONCLUSIONS

In this study, micronized griseofulvin has been used effectively in the treatment of 49 patients with superficial mycotic infections due to *Microsporum audouini*, *Microsporum canis* and *Trichophyton rubrum*.

The results obtained indicate that a 0.5 gm. daily oral dose of micronized griseofulvin will produce the same therapeutic results obtained by the use of a 1 gm. daily dose of the standard common grade griseofulvin.

Adverse reactions were minimal. One patient complained of severe headache while taking micronized griseofulvin but did not experience the same reaction while taking the common variety.

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